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Identification of Women With T1–T2 Breast Cancer at Low Risk of Positive Axillary Nodes

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Background and Objectives: The diagnostic and therapeutic significance of axillary dissection has been questioned. We sought to define a subgroup of patients with early-stage breast cancer who are at low risk for positive axillary nodes.

Methods: Between 1970 and 1995, 1,598 women with stage I and II breast cancer underwent level I-II axillary dissection with a minimum of 10 nodes removed. The following factors were examined in univariate analysis for predicting positive nodes: race, method of detection, location of the primary tumor, age, menopausal status, obesity, ER status, PR status, pathologic tumor size, lymphatic vascular invasion, tumor grade, and histology.

Results: Four hundred and forty-five of the 1,598 patients (27.8%) had histologically positive axillary nodes. Significant factors in univariate analysis for positive nodes included: tumor size, lymphatic vascular invasion, grade, method of detection, primary tumor location, and age. The only group of women with a 0% risk of axillary nodes were those in whom the pathologic tumor size was ≤5 mm and mammographically detected. A 5–10% risk of positive axillary nodes was identified in women with (1) pathologic tumor size 6–10 mm, mammographically detected, and age ≤40 years, and (2) tubular carcinoma ≤10 mm. Tumors detected on physical examination with or without mammography and women ≤40 years had a significantly increased risk of nodes. In multivariate analysis lymphatic vascular invasion ($P < 0.001$), method of detection ($P = 0.026$), location ($P = 0.01$), and pathologic tumor size ($P = 0.002$) were significant predictors of positive axillary lymphadenopathy.

Conclusions: The decision to forego an axillary dissection should be considered in (1) tumors mammographically detected and ≤5 mm (2) mammographically detected, pathologic size 6–10 mm, age >40 and (3) tubular carcinoma ≤10 mm. All other groups had a >10% risk of nodes and may benefit from axillary dissection.

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INTRODUCTION

Axillary lymph node involvement is the most important prognostic factor for overall survival and disease-free survival in early-stage breast cancer and determines the necessity of adjuvant treatment including chemotherapy and/or hormonal treatment. Axillary dissection has also proven effective in preventing local recurrence in the axilla [1,2]. Clinical examination of the axilla has yielded both false-positive and -negative results in approximately 30% of cases [3–5]. However, axillary dissection is associated with a 10% incidence of minor complications, including shoulder dysfunction, breast edema, arm edema, wound infection, and seroma formation. Thus, it would prove beneficial if a group of women with a low risk of axillary lymphadenopathy could be identified so that dissection could be avoided.

METHODS AND MATERIALS

Between March 1970 and March 1995, 1,598 women with American Joint Committee on Cancer [6] stage I and II breast cancer underwent excisional biopsy, a level I–II axillary dissection, and definitive irradiation at the Fox Chase Cancer Center (987 patients) and by one of the authors (BLF) at the Hospital of the University of Pennsylvania (611 patients) [6]. The criteria for selection of potential candidates for definitive irradiation, as well as surgical and radiotherapeutic techniques have been described previously [7,8]. Not included in this analysis were 97 women who did not undergo an axillary dissection and 234 women who did not have ⩾10 nodes removed.

Patient and tumor characteristics are presented in Tables I and II. One thousand and eight-two (67.7%) had clinical T1 tumors and 516 (33.3%) had clinical T2 tumors. Pathological size of the tumor ranged from 0 to 5 cm (median 3 cm). Pathologic size of the primary tumor was divided into the following categories: 0–5 mm (68 patients, 4.3%), 6–10 mm (306 patients, 19.1%), 11–20 mm (627 patients, 39.2%), 21–30 mm (251 patients, 15.7%), 31–40 mm (91 patients, 5.7%), and 41 to 50 mm (14 patients, 1%) and unknown (241 patients, 15.1%). Tumor histology, estrogen receptor (ER) status, and progesterone receptor (PR) status are reported in Table I. In addition, the incidence of lymphatic vascular space invasion, nuclear grade, and histologic grade are noted in Table I.

The method of detection, the location of the primary tumor, and the patient's race are noted in Table II. Of the tumors detected by mammography alone, 83 (17.0%) presented with microcalcifications alone, 333 (68.4%) with a mass, and 59 (12.1%) with a combination of a mass and microcalcifications. Age, menopausal status, and Quetelet's index are also reported in Table II.

In the analysis of the following prognostic factors each was initially examined separately using the χ^2 test [9]: ER status, PR status, race, pathologic tumor size, lymphatic vascular invasion, tumor grade, method of tumor detection, location of the primary tumor, age, menopausal status, histology and Quetelet's index. A simultaneous examination of the factors found to be significant in univariate analysis was made using logistic analysis [10]. The parameters included as covariates were ER status (positive vs. negative), PR status (positive vs. negative), race (African-American vs. white), pathologic tumor size (0–5 mm vs. 6–10 mm vs. 11–20 mm vs. 21–30 mm vs. 31–40 mm vs. 41–50 mm), lymphatic vascular invasion (present vs. absent), grade (high or medium vs. low), method of detection (mammography alone vs. physical examination with or without mammography), location of the primary tumor (outer vs. central, inner or subareolar), age (⩽40 vs. >40 years), menopausal status (premenopausal vs. perimenopausal vs. postmenopausal), histology (invasive ductal plus intraductal carcinoma vs. invasive ductal vs. invasive lobular or invasive lobular and invasive ductal vs. other), Quetelet's index (⩽3.2 vs. 3.3–4.0 vs. >4.0), and tumor grade (high vs. intermediate vs. low). In both the univariate and multivariate analyses, patients with unknown factors were excluded.

RESULTS

Four hundred and forty-five of the 1,598 patients (27.8%) had histologically positive axillary nodes (Tables I, II). Univariate analyses revealed significant differences in nodal positivity for the following variables: lymphatic vascular invasion, histologic grade, method of detection, primary tumor location, age, and pathologic tumor size. Specifically, 79 of the 159 patients (49.7%) with lymphatic vascular space invasion had positive nodes while only 66 of 290 patients (22.8%) without lymphatic vascular invasion had positive axillary nodes ($P = 0.001$). The grade of the tumor also significantly influenced the incidence of nodes as 10.6% of patients with low grade tumors had positive nodes, compared to 25.9% with intermediate grade tumors and 30.0% with high-grade tumors ($P = 0.001$). Similarly, the method of tumor detection had an impact on the incidence of positive nodes. Of the patients whose primary was detected by mammographic findings alone, 15.8% had positive nodes compared to 33.1% and 32.5%, respectively, among patients whose tumor was detected by physical examination alone or a combination of physical examination and mammographic findings ($P = 0.001$). Patients whose tumor was located in the outer

TABLE I. Tumor Pathologic Features and Nodal Status

Variable	Total no. of patients	No. of patients with positive nodes	P^a
ER receptor status			
Positive	977 (61.1%)	293 (30.0%)	0.99
Negative	342 (21.5%)	103 (30.0%)	
Unknown	278 (17.4%)	48 (17.3%)	
PR receptor status			
Positive	797 (49.9%)	244 (30.6%)	0.39
Negative	454 (28.3%)	128 (28.3%)	
Unknown	349 (21.8%)	72 (20.6%)	
Lymphatic vascular invasion			
Present	159 (9.9%)	79 (49.7%)	0.001
Absent	290 (18.1%)	66 (22.8%)	
Unknown	1149 (71.9%)	299 (26.0%)	
Nuclear grade			
Low	59 (3.7%)	12 (20.3%)	0.001
Moderate	146 (9.1%)	36 (24.7%)	
High	232 (14.5%)	65 (28.0%)	
Unknown	1161 (72.6%)	331 (28.5%)	
Histologic grade			
Low	85 (5.3%)	9 (10.6%)	0.001
Moderate	274 (17.1%)	71 (25.9%)	
High	466 (29.2%)	140 (30.0%)	
Unknown	773 (48.4%)	224 (29.0%)	
Histologic subtype			
DCIS + invasive ductal	812 (50.1%)	229 (28.2%)	0.10
Invasive ductal	607 (38.0%)	175 (28.8%)	
Invasive lobular	67 (4.2%)	13 (19.4%)	
Invasive lobular + invasive ductal	33 (2.1%)	25 (75.8%)	
Medullary	32 (2.0%)	11 (34.4%)	
Colloid	12 (1.0%)	1 (8.3%)	
Tubular	25 (1.6%)	3 (12.0%)	
Other	10 (1.0%)	0 (0%)	
Pathologic tumor size			
0–.5 cm	68 (4.3%)	6 (8.8%)	0.001
0.6–1.0 cm	306 (19.1%)	40 (13.1%)	
1.1–2.0 cm	627 (39.2%)	162 (25.8%)	
2.1–3.0 cm	251 (15.7%)	98 (39.0%)	
3.1–4.0 cm	91 (5.7%)	42 (46.2%)	
4.1–5.0 cm	14 (1%)	8 (57.1%)	
Unknown	241 (15.1%)		

[a]In the determination of *P* values, patients with unknown factors were excluded.

TABLE II. Patient Characteristics and Nodal Status

Variable	Total no. of patients	No. of patients with positive nodes	P^a
Method of detection			
Physical examination	332 (20.1%)	110 (33.1%)	0.001
Mammogram	487 (30.5%)	77 (15.8%)	
Physical exam + mammogram	758 (47.4%)	246 (32.5%)	
Unknown	21 (1.3%)		
Location			
Outer	924 (57.9%)	302 (32.7%)	0.001
Central	275 (17.2%)	59 (21.4%)	
Inner	324 (20.3%)	65 (20.1%)	
Subareolar	73 (4.6%)	17 (23.3%)	
Race			
African-American	140 (8.9%)	45 (32.1%)	0.23
White	1441 (90.2%)	395 (27.4%)	
Other	17 (1.1%)		
Age			
⩽40	224 (14.0%)	76 (33.9%)	0.02
41–50	393 (24.6%)	118 (24.6%)	
>50	981 (61.4%)	250 (25.5%)	
Menopausal status			
Premenopausal	523 (32.7%)	160 (30.6%)	0.10
Perimenopausal	94 (5.9%)	30 (31.9%)	
Postmenopausal	981 (61.4%)	254 (25.9%)	
Quetelet's index			
⩽3.2	323 (20.2%)	98 (30.3%)	0.29
3.3–4.0	531 (33.3%)	137 (25.8%)	
>4.0	345 (21.6%)	89 (25.8%)	
Unknown	399 (25.0%)		

[a]In the determination of *P*-values, patients with unknown factors were excluded.

quadrant of the breast had a significantly higher incidence of positive nodes compared to individuals who presented with a primary tumor which involved the central, inner, or subareolar aspects of the breast. Specifically, 32.7% of patients with a primary tumor of the outer aspect of the breast had positive nodes compared to 21.4% for tumors of the central aspect, 20.1% for inner quadrant tumors, and 23.3% for subareolar tumors ($P = 0.001$).

The incidence of positive axillary nodes was inversely proportional to age. Seventy-six of 224 patients (33.9%) ⩽40 years had positive nodes compared to 118 of 393 patients (24.6%) age 41–50, and 250 of 981 patients (25.5%) >50 years ($P = 0.02$). Pathologic tumor size was an important predictor of nodal positivity as there was a direct relationship between tumor size and the incidence of positive axillary nodes. Pathologic tumor size was associated with positive nodes as follows: 0.0–0.5 cm, 8.8%; 0.6–1.0 cm, 13.1%; 1.1–2.0 cm, 25.8%; 2.1–3.0 cm, 39.0%; 3.1–4.0 cm 46.2%; and 4.1–5.0 cm, 57.1% ($P = 0.001$). Patients with tumors ⩽0.5 cm detected on physical examination with or without mammography had a 20% incidence of positive nodes. The other variables that were examined in univariate analysis did not significantly influence the incidence of positive nodes (Tables I, II).

Multivariate analysis was performed using the endpoint of nodal status. In the analysis of the influence of the following prognostic factors on nodal status, each was initially examined separately using the Pearson chi-square test [9]: lymphatic vascular invasion (present vs. absent), tumor grade (low vs. intermediate or high), method of detection (mammographic only vs. physical examination or physical examination plus mammographic), pathologic tumor size (<1 cm vs. 1.1–2.0 cm vs. 2.1–5.0 cm), age (⩽40 years vs. 41–50 years vs. >50 years), and location (outer vs. central, inner or subareo-

lar). The following variables significantly influenced the incidence of positive nodes: lymphatic vascular invasion ($P < 0.001$), method of detection ($P = 0.026$), location of the primary tumor ($P = 0.009$), and pathologic tumor size ($P = 0.002$). Stepwise linear logistic regression was used to assess these associations while adjusting for other covariates [10]. Specifically, patients with an increased incidence of positive nodes had lymphatic space invasion, presented with primary tumors which were detected on physical examination or a combination of physical examination and mammographic findings, had tumors in the outer quadrant of the breast, and tumors >2.0 cm.

Subgroup analysis was performed on the 1,419 patients with invasive ductal carcinoma with or without DCIS to better define a group of patients who are at low risk of positive axillary nodes. Patients with a pathologic tumor size ≤5 mm which was mammographically detected had a 0% incidence of positive axillary nodes. By contrast, in patients with a pathologic tumor size ≤5 mm detected on physical examination plus mammography, the incidence of positive nodes increased to 20%. For patients with a pathologic tumor size ≤10 mm which was mammographically detected the incidence of positive axillary nodes was 8.9%. A similar analysis which included patients with a pathologic tumor size ≤10 mm, mammographically detected, and ≤40 years old revealed a 33% incidence of positive axillary nodes. A separate analysis of women with tubular carcinoma revealed that tumors ≤10 mm had a 10% incidence of nodes while those >10 mm had a 14% incidence of positive nodes.

DISCUSSION

Axillary dissection is routinely performed in patients with T1–T2 invasive breast carcinoma as the status of the axilla is important in directing adjuvant chemotherapy and hormonal treatment and/or radiation therapy. Furthermore, it is unlikely that therapeutic doses of radiation therapy can control positive axillary nodes without significant morbidity including lymphedema. The incidence of axillary failure in initially N0 patients has ranged from 13% to 37% for individuals who had inadequate axillary dissection or substandard radiotherapy [1,11–13]. A trial from 2 Danish hospitals demonstrated that the probability of finding at least one positive axillary node increased continuously up to 10 nodes removed [14]. Kiricuta and Tausch [15] developed a mathematical model in which it was demonstrated that 10 negative axillary nodes from level I would provide a 90% probability that no other nodes are involved at other levels. Thus, in our study only patients who had ≥10 nodes removed were included.

The axilla comprises the primary site of drainage of the breast. Most surgeons continue to dissect only level I and II nodes, as Pigott et al. [16] and Smith et al. [17] demonstrated that only 3.1% and 9.9%, respectively, of patients had metastases to level III alone. Complications of axillary dissection include arm edema, nerve damage, decreased shoulder mobility, seroma formation, wound infection and breast edema. The risk of significant arm edema without subsequent radiation therapy to the axilla after level I–II axillary dissection is ≤5% [18].

Owing to the potential morbidity of axillary dissection, it would be beneficial to define a subgroup of patients who have <10% risk of positive axillary nodes and would not benefit from a level I–II dissection. A number of investigators have correlated tumor size with the likelihood of negative lymphadenopathy [19–25]. In our study, pathologic tumor size significantly influenced the incidence of positive axillary nodes in both univariate and multivariate analysis (Table I). Reger et al. [21] assessed 626 women who underwent axillary dissection for breast tumors of ≤2 cm. Tumor size correlated significantly with the incidence of positive axillary metastases ($P = 0.000001$). Patients with tumors measuring 0.0–0.5 cm had a 3% incidence of positive nodes compared to 10% for tumors 0.6–1.0 cm, 21% for 1.1–1.5 cm, and 35% for 1.6–2.0 cm [21]. Seidman et al. [22] noted that the incidence of positive axillary nodes was directly related to the size of the invasive component of the tumor [22]. Specifically, 0% of tumors <0.5 cm had positive nodes compared to 22% of tumors of 0.51–1.0 cm, 55% of tumors 1.1–1.5 cm, 80% of tumors 1.5–2.0 cm, and 100% for tumors 2.01–3.0 cm. Silverstein et al. [23] confirmed that the size of the primary tumor was directly related to the incidence of positive axillary nodes. Specifically, he reported that the incidence of positive axillary nodes by T stage was as follows: T1a, 3%; T1b, 17%; T1c, 32%; T2, 44%; and T3, 60%.

Walls et al. [25] noted that tumors <1 cm had a 3% incidence of positive axillary nodes. Tinnemans et al. [24] reported in a review of women with clinically occult breast carcinoma that tumors measuring ≤5 mm, 6–10 mm and >10 mm had an incidence of nodal positivity of 7.7%, 12.5%, and 29.5%, respectively. Chadha et al. [19] noted that only 9% of patients with primary tumors ≤1 cm and no evidence of lymphovascular invasion had positive axillary nodes. Lin et al. [26] reported that 13% of patients with clinically negative nodes and favorable primary biopsies (ER and PR positive, tumor size <2 cm, diploid with percentage S phase <5.8 or aneuploid with percentage S phase <3.4) had histologically positive axillary nodes [26]. The only subgroup that could be identified with a <10% risk of positive axillary nodes were patients with primary tumors <0.5 cm. Halverson et al. [20] reported that 0% of patients with primary tumors <5 mm had positive nodes compared to 14.7% with tumors

6–10 mm. Furthermore, axillary nodes were histologically positive in only 3% of patients with tumors ≤1.0 cm who presented with primary tumors involving the central and inner quadrants, and in 8% and 7% of well- and moderately differentiated tumors, respectively.

Other investigators have reported that a low incidence of axillary nodes is dependent upon other factors including histology, the palpability of the primary tumor, and tumor grade [23,25,27–29]. Silverstein et al. [23] reported that palpable and nonpalpable T1a tumors had a 4% and 5% incidence of nodal positivity. Schwartz et al. [28] noted that 27.5% of patients presenting with nonpalpable clustered microcalcifications alone had histologically positive nodes compared to 26.9% of patients who presented with a mass, a mass with associated microcalcifications, or parenchymal distortion. Walls et al. [25] noted that in multiple logistic regression analysis, pathological tumor size, tumor grade and the absence of mammographic microcalcifications were independently predictive of axillary nodes. Other workers have reported that outer quadrant tumors are associated with a higher incidence of positive nodes [1,29]. In our study, tumor location and the method of detection were significant predictors of nodal positivity in both univariate and multivariate analysis (Tables I, II).

The value of axillary dissection in early breast carcinoma remains controversial. Cabanes et al. [30] from the Institut Curie randomized patients with primary breast tumors <3 cm and no clinically positive axillary nodes to treatment with either lumpectomy alone followed by irradiation of the axillary and internal mammary nodes or lumpectomy and axillary dissection followed by irradiation of the internal mammary nodes [30]. There was a significant survival advantage for patients undergoing axillary dissection. Four randomized trials have demonstrated a reduction in local recurrence for patients treated with mastectomy and axillary dissection with or without axillary irradiation, compared to mastectomy and axillary irradiation alone [1,12,30,31].

We continue to recommend level I–II axillary dissection for all women except those who present with a primary tumor ≤0.5 cm that are mammographically detected. This group of patients had a 0% incidence of positive axillary nodes. Strong consideration should be given to foregoing axillary dissection to two groups of women with a 5–10% incidence of positive nodes: (1) mammographically detected, pathologic tumor size 6–10 mm and age >40 years; and (2) tubular carcinoma ≤10 mm. All other groups of women had an incidence of positive axillary lymphadenopathy exceeding 10% and thus would potentially benefit from an axillary dissection to help determine the necessity of adjuvant treatment, as well as eradicate microscopic disease.

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